

WEEK 24 IS THE OPTIMAL TIME POINT FOR PREDICTING OUTCOMES AT 2 YEARS WITH TELBIVUDINE

K. Rajender Reddy,¹ Vinod K. Rustgi,² Stefan Zeuzem,³ Edward Gane,⁴ Seng Gee Lim,⁵ Ji-Dong Jia,⁶ Bruce Belanger,⁷ Shelley George,⁷ George Harb⁸

¹University of Pennsylvania School of Medicine, Philadelphia, PA, USA; ²Georgetown University School of Medicine, Washington, DC, USA; ³Saarlant University Hospital, Homburg, Germany; ⁴Middlemore Hospital, Otahuhu, Auckland, New Zealand;

⁵National University Hospital, Singapore; ⁶Beijing Friendship Hospital, Beijing, China; ⁷Idenix Pharmaceuticals, Cambridge, MA, USA; ⁸Novartis Pharmaceuticals Inc., East Hanover, NJ, USA

Background

- The degree of viral suppression achieved during treatment of chronic hepatitis B infection, as measured by hepatitis B virus (HBV) DNA levels, appears to be the most important predictor of long-term outcomes. The degree of HBV DNA reduction early in the course of treatment with nucleos(t)ide analogs is highly predictive of outcomes at 1 and 2 years.¹
- Not all patients achieve durable viral suppression. For several anti-HBV agents, suboptimal initial response is associated with increased risk of subsequent resistance.^{1,2}
- Early monitoring of the virologic response to treatment in chronic hepatitis B may be useful to identify suboptimal responses, allowing the clinician to modify treatment accordingly.¹
- The large phase III GLOBE study, which compared the efficacy and safety of telbivudine 600 mg/day and lamivudine 100 mg/day in 1367 adult patients with chronic hepatitis B, is a randomized, double-blind, controlled trial providing 2-year clinical outcomes based on the intent-to-treat population. After both 1 and 2 years, telbivudine demonstrated significantly greater efficacy compared with lamivudine on all direct measures of antiviral efficacy.³ The GLOBE study provides a robust database for assessing factors that may contribute to long-term clinical outcomes for both hepatitis B e-antigen (HBeAg)-positive and HBeAg-negative patients.

Aim

- The goal of the current analyses is to identify the best early time point for predicting long-term efficacy outcomes in patients treated with telbivudine.

Methods

- The GLOBE study enrolled nucleos(t)ide-naïve patients aged 16–70 years with HBeAg-positive (n=921) or HBeAg-negative (n=446) compensated chronic hepatitis B.³
- All patients treated with telbivudine 600 mg daily were included in an analysis of receiver operating characteristic (ROC) curves for HBV DNA viral load at 4, 8, 12, 24, and 32 weeks of therapy. The ROC curve is commonly used for evaluating the usefulness of a biomarker in the clinical diagnosis and treatment of disease. A ROC curve is a plot of a test's sensitivity, as a function of 1 minus specificity, across a range of all possible cut-points (decision threshold values).
- Two methods commonly used for establishing the "optimal" cut-point are the point on the ROC curve closest to (0,1) and the Youden index, *J*, the latter being appropriate for analyses where there are samples below the limit of detection.^{4,5} The Youden index, *J*, is the maximum vertical distance from the ROC curve to the line of identity, or chance line (ie, where the curve would lie if there were no relationship between predictor and outcome), and identifies the threshold value of the test that is associated with the greatest discrimination of outcome. Values close to one indicate that the biomarker's effectiveness is relatively large; values close to zero indicate limited effectiveness.
- Study endpoints assessed in this analysis included serum HBV DNA reduction, HBeAg seroconversion, and resistance. Serum HBV DNA was quantified by COBAS® Amplicor polymerase chain reaction (PCR) assay (detection limit 300 copies/mL). Resistance was defined as viral breakthrough (increase of serum HBV DNA ≥1 log above nadir) with confirmed genotypic resistance, based on the full length DNA sequencing of the reverse transcriptase domain of HBV polymerase.

- Multivariate regression analyses were used to identify and assess baseline and early on-treatment (Weeks 24) variables predictive of Week 104 efficacy outcomes. Baseline variables included in the model were age, body mass index, alanine aminotransferase (ALT), fibrosis Ishak score, serum HBV DNA, Knodell histologic activity index (HAI) score, gender, and HBV genotype. Continuous variables were dichotomized along the median of HBeAg-positive and HBeAg-negative groups. *P*-values <0.15 were required for model entry and >0.25 for model exit.
- ROC curves were constructed to evaluate the predictive value of HBV DNA levels at baseline and at 4, 8, 12, 24, and 32 weeks of therapy on each of the specified 2-year outcomes. Each ROC analysis included only patients who had an observed value of the prognostic test; missing data were considered as failures for the 2-year outcomes.
- To investigate the clinical relevance of HBV DNA levels at various time points (Weeks 8, 12, 24, and 32), we calculated positive predictive value (PPV, % response if the test is normal), negative predictive value (NPV, % non-response if test is abnormal), sensitivity (% response identified by test), and specificity (% non-response identified by test) at the Youden index HBV DNA threshold for the Week 104 outcomes of serum HBV DNA undetectability (<300 copies/mL), emergence of resistance, and HBeAg seroconversion (in HBeAg-positive patients only).

Results

HBeAg-Positive Patients

- For HBeAg-positive patients treated with telbivudine, the sensitivity, specificity, PPV, and NPV values for Week 4, 8, 12, 24, and 32 serum HBV DNA levels for the prediction of Week 104 outcomes at the Youden index threshold are presented in Table 1. At the early (Weeks 4, 8, and 12) time points, the predictive sensitivity of PCR-negativity for all outcomes is relatively low, and specificity is high. At Weeks 24 and 32, sensitivity is substantially higher, consistent with the marked increase in PCR-negativity at those points, and specificity is only marginally reduced, vs. Week 12.

Table 1. Sensitivity and specificity, positive and negative predictive values: for Week 4, 8, 12, 24, and 32 serum HBV DNA levels as predictor of Week 104 outcomes (HBeAg-positive telbivudine recipients)

Week (n)	4 (30)				8 (30)				12 (84)				24 (202)				32 (251)			
Week 104 outcome	Sens	Spe	PPV	NPV	Sens	Spe	PPV	NPV	Sens	Spe	PPV	NPV	Sens	Spe	PPV	NPV	Sens	Spe	PPV	NPV
Serum HBV DNA undetectable	0.64	0.70	0.73	0.60	0.62	0.78	0.78	0.61	0.70	0.77	0.79	0.66	0.78	0.73	0.79	0.71	0.81	0.74	0.81	0.75
Lack of resistance	0.57	0.76	0.87	0.38	0.56	0.77	0.88	0.37	0.60	0.8	0.9	0.41	0.63	0.78	0.89	0.42	0.69	0.76	0.89	0.45
HBeAg seroconversion	0.83	0.43	0.38	0.86	0.59	0.72	0.47	0.8	0.71	0.63	0.45	0.84	0.84	0.55	0.44	0.89	0.89	0.52	0.45	0.92

¹Number of patients achieving serum HBV DNA <300 copies/mL at each time point.
Sens, sensitivity; Spe, specificity.

Table 2. Youden's indices *J* and discrimination threshold for serum HBV DNA levels at Week 4, 8, 12, 24, and 32 as predictors of Week 104 outcomes, HBeAg-positive, telbivudine treated patients, GLOBE trial

Week	4		8		12		24		32	
Week 104 outcomes	Index <i>J</i>	Threshold	Index <i>J</i>	Threshold	Index <i>J</i>	Threshold	Index <i>J</i>	Threshold	Index <i>J</i>	Threshold
Serum HBV DNA undetectable	0.340	5.09	0.396	4.07	0.463	3.56	0.505	2.87	0.554	2.60
Lack of resistance	0.330	5.11	0.331	4.18	0.398	3.56	0.415	2.74	0.442	2.60
HBeAg seroconversion	0.262	5.67	0.302	3.93	0.342	3.52	0.389	3.06	0.411	2.89

The Youden's index, *J*, is the maximum value of (sensitivity + specificity - 1) obtained under the ROC curve, the threshold is the log₁₀ serum HBV DNA level at which this maximum *J* index is obtained.

- The Youden index, *J*, and discrimination threshold for HBV DNA levels at Weeks 4, 8, 12, 24, and 32 as predictors of Week 104 outcomes are shown in Table 2. The associated ROC curves for Weeks 8, 12, and 24 are shown in Figure 1. The Youden index, *J*, increases consistently across all outcomes from Week 4 through Week 32, while the threshold at which the maximal distance is achieved decreases. Thus, Week 24 is a more reliable predictor of Week 104 outcomes than earlier time points, providing a favorable balance between sensitivity and specificity for identifying patients at risk of negative 2-year outcomes.
- Based on a logistic regression model of baseline characteristics, baseline HBV DNA level (<9 log₁₀ copies/mL) was the strongest predictor of undetectable HBV DNA by Week 24 (Figure 2).

Figure 1. Comparison between Week 24 and Weeks 8 and 12 serum HBV DNA Youden index to predict Week 104 serum HBV DNA undetectability, HBeAg-positive patients.

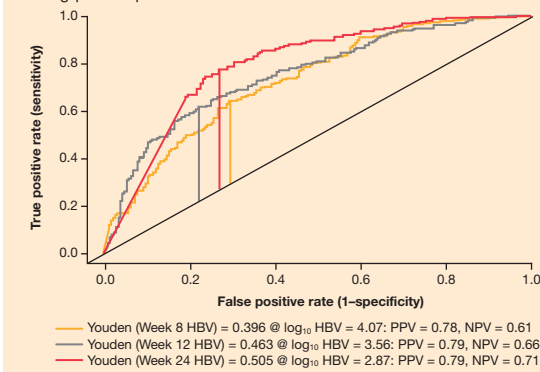


Table 3. Sensitivity and specificity, positive and negative predictive values: for Week 8, 12, 24, and 32 serum HBV DNA levels as predictor of Week 104 outcomes (HBeAg-negative telbivudine recipients)

Week (n)	4 (67)				8 (67)				12 (107)				24 (177)				32 (187)			
Week 104 outcome	Sens	Spe	PPV	NPV	Sens	Spe	PPV	NPV	Sens	Spe	PPV	NPV	Sens	Spe	PPV	NPV	Sens	Spe	PPV	NPV
Serum HBV DNA undetectable	0.83	0.45	0.87	0.37	0.69	0.6	0.89	0.3	0.69	0.65	0.9	0.31	0.87	0.46	0.88	0.44	0.98	0.35	0.88	0.76
Lack of resistance	0.82	0.58	0.94	0.29	0.7	0.75	0.96	0.23	0.68	0.79	0.96	0.23	0.87	0.62	0.95	0.37	0.97	0.46	0.94	0.65

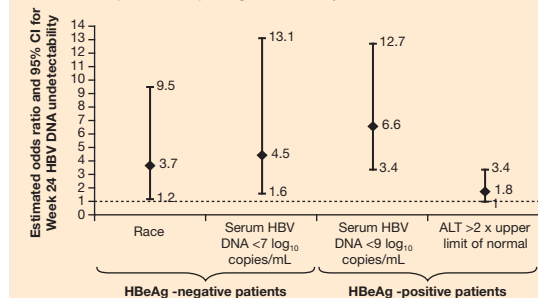
¹Number of patients achieving serum HBV DNA <300 copies/mL at each time point.

Table 4. Youden's indices *J* and discrimination threshold for serum HBV DNA levels at Week 4, 8, 12, 24, and 32 as predictors of Week 104 outcomes, HBeAg-negative, telbivudine treated patients, GLOBE trial

Week	4		8		12		24		32	
Week 104 outcomes	Index <i>J</i>	Threshold	Index <i>J</i>	Threshold	Index <i>J</i>	Threshold	Index <i>J</i>	Threshold	Index <i>J</i>	Threshold
Serum HBV DNA undetectable	0.280	4.93	0.292	3.42	0.335	2.79	0.335	2.53	0.329	3.23
Lack of resistance	0.407	4.93	0.452	3.50	0.467	2.79	0.493	2.53	0.427	3.23

The Youden's index, *J*, is the maximum value of (sensitivity + specificity - 1) obtained under the ROC curve, the threshold is the log₁₀ serum HBV DNA level at which this maximum *J* index is obtained.

Figure 2. Baseline characteristics associated with Week 24 serum HBV DNA undetectability among telbivudine-treated patients (GLOBE study), based on stepwise multiple regression analyses.



HBeAg-Negative Patients

- For HBeAg-negative patients treated with telbivudine, the sensitivity, specificity, PPV, and NPV values for Week 4, 8, 12, 24, and 32 serum HBV DNA levels for the prediction of Week 104 outcomes at the Youden index threshold are presented in Table 3. Similar to the trend for HBeAg-positive patients, sensitivity increases and specificity decreases at the later time points, Weeks 24 and 32.
- The Youden index, *J*, and discrimination threshold for HBV DNA levels at Weeks 4, 8, 12, 24, and 32 as predictors of Week 104 outcomes are shown in Table 4. Consistent with the results in HBeAg-positive patients, the Youden index, *J*, increases consistently across all outcomes from Week 4 through Week 24, while the threshold at which the maximal distance is achieved decreases. Beyond Week 24, the Youden index, *J*, decreases for prediction of HBV DNA undetectability and lack of resistance emergence at Week 104, while the threshold at which the Youden index is calculated increases from Week 24 for both parameters.
- The only baseline characteristic associated with the probability of achieving undetectable HBV DNA by Week 24 was baseline serum DNA level (<7 log₁₀ copies/mL) (Figure 2).

Outcomes at Week 104 of Patients Reaching Serum HBV DNA Undetectable by Week 12, 24, or 32

- Week 24 serum HBV DNA levels ensure a higher predictability of favorable clinical outcomes than earlier time points for both HBeAg-positive and HBeAg-negative patients. Although time points up to Week 12 have a high PPV (ie, patients with an early virologic response have a high probability of achieving favorable outcomes by Week 104), they also have a poor NPV (ie, patients without an early virologic response do not have a high probability of treatment failure by Week 104).
- Patients who do not achieve serum HBV DNA undetectable until Week 32 have outcomes less optimal than those reaching this endpoint at Week 24, and are at greater risk of developing resistance (data not shown).

Conclusions

- This analysis identifies clinically useful predictors of response to telbivudine, both at baseline and on therapy, providing a tool to guide treatment decisions.
- Serum HBV DNA level at baseline is the best predictor of Week 24 response. HBeAg-positive and HBeAg-negative patients with HBV DNA prior to treatment of <9 and <7 log₁₀ copies/mL, respectively, are more likely to achieve undetectable HBV DNA levels at Week 24.
- Moreover, evaluation of serum HBV DNA at Week 24 is a reliable, clinically meaningful predictor of Week 104 outcomes, including serum HBV DNA undetectability (<300 copies/mL), emergence of resistance, and HBeAg seroconversion (in HBeAg-positive patients).
- Week 24 is the best time point to assess initial response to telbivudine therapy as it provides a favorable balance of sensitivity and specificity for identifying patients at risk of negative outcomes at 2 years. Clinical decisions to either continue or modify therapy are optimally made at Week 24.
- By combining baseline and Week 24 serum HBV DNA assessments, clinicians can better identify patients likely to be the best candidates for telbivudine therapy and can make better decisions regarding continuation or modification of the therapeutic regimen.

References

- Keefe EB et al. *Clin Gastroenterol Hepatol.* 2007;5:890-897.
- Rustgi VK et al. *Future Virology.* 2007;2:79-90.
- Lai C-L et al. *Hepatology.* 2006;44(suppl 1):222A (Abstract 91).
- Perkins NJ et al. *Am J Epidemiol.* 2007;165:325-333.
- Youden WJ. *Cancer.* 1950;3:32-35.